39. (new) A composition according to claim 38 in unit dosage form.

40. (new) A composition according to claim 37, wherein said carrier is an isotonic solution.

REMARKS

Favorable consideration and allowance are respectfully requested for claims 1-40 in view of the following remarks.

New claims 35-36 and 37-40 are at least supported by claims 1-2 and 22-25, respectively. No new matter has been added.

In the Office Action dated September 25, 2002, claims 22-25 were objected to; claims 5-21 and 26-33 were rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement; claims 1-21 and 26-34 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite; claims 1, 3-9 and 14-18 were rejected under 35 U.S.C. § 102(a) as being anticipated by WO 01/10842 ("Maguire"); claims 1, 3-9 and 14-18 were rejected under 35 U.S.C. § 102(b) as being anticipated by Chem. Abstract 112:35878 (1990) ("Kolaczkowska") and GB 2082577 ("Frei"); claim 1 was rejected under 35 U.S.C. § 102(b) as being anticipated by Chem. Abstract 87:179949 ("Kwok"); and claims 1, 3-21, and 26-34 were rejected under 35 U.S.C. § 102(b) as being anticipated by Chem. Abstract 87:111268 ("Walker") and Chem. Abstract 77:70055 ("Upshall"). These rejections are respectfully traversed.

Objection to Multiple Dependency

Claims 22-25 have been modified to depend from claim 3 and have been substantially duplicated as claims 37-40, which depend from claim 4. Accordingly, withdrawal of the objection is requested.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 5-21 and 26-33 were rejected because the specification, while being enabling for the treatment of depression and anxiety, allegedly "does not reasonably

provide enablement for preventing or treating [ ] all types of cerebral circulation diseases, neurodegenerative diseases, etc."

The present specification reasonably provides various biological activities of the compounds of the claimed invention. In the specification, the binding assay of two types of nicotinic acetylcholine receptor is described; that is, $\alpha 4\beta 2$ subtype and $\alpha 1\beta 1\gamma$ subtype of nicotinic acetylcholine receptor are set forth, particularly in the Biological Experiments 1 and 2.

Further, the specification describes the relationship between the role of nicotinic acetylcholine receptor and various kinds of disease, for example, Alzheimer's disease, neurodegenerative disease such as Parkinson's disease, neuroses and psychoses such as dementia, anxiety, schizophrenia and so on. The specification also sets forth the fact that development studies for selective agonists or modulators at the nicotinic acetylcholine receptor of central nervous system act as practical medicine.

The specification discusses that the compound ABT-418 is a selective agonist at the nicotinic acetylcholine receptor and is under development as a practical medicine. See page 5, lines 4-5. Notably, ABT-418 shows the same biological effects as the compounds of the claimed invention. ABT-418 is the first novel selective nicotinic agonist tested on human patients. In a placebo-controlled design study, ABT-418 showed significant dose-related improvement in learning and memory in early to moderate stages of Alzheimer's disease patients. The specification describes that the claimed compounds demonstrate the same selective agonist effect at the nicotinic acetylcholine receptor as ABT-418.

In support, Applicants submit a Declaration pursuant to 37 C.F.R. 1.132 of Dr. Tani ("Declaration"). In the Declaration, Dr. Tani, one of the present inventors, declared the conventional knowledge as follows (see Declaration at 2):

> Clinical studies indicate that (-) –nicotine may be beneficial for treatment of impairment in attention and rapid information processing with Alzheimer's disease, and imply that not only the cholinergic systems but also monoaminergic systems are possible mechanisms by

> which (-) -nicotine treatment improves cognitive performance. Among the monoaminergic systems, it has been suggested that noradrenergic effects of stimulants as important therapeutic mechanisms on enhancing capacities such as attention and working memory.

As stated above, the binding assays of the $\alpha 4\beta 2$ subtype and $\alpha 1\beta 1\gamma$ subtype of nicotinic acetylcholine receptors were discussed in the Biological Experiments 1 and 2. Based on these Biological Experiments, Dr. Tani further declared the experiment results for the effects of the compounds of the claimed invention on norepinephrine (NE) turnover in the mouse whole brain as the first *in vivo* assay, in comparison with the known nicotinic receptor agonist such as (-) -nicotine and ABT-418. See Declaration at 2-5. As set forth in the Declaration, the compounds of the claimed invention show a significant effect compared to (-)-nicotine and ABT-418.

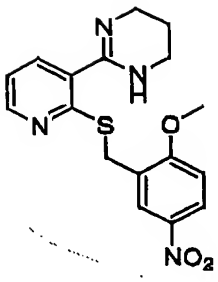
Accordingly, a person having ordinary skill in the art would understand that the specification provides reasonable enablement for the claimed invention. Withdrawal of the rejection of claims 5-21 and 26-33 under 35 U.S.C. §112, first paragraph, is respectfully requested.

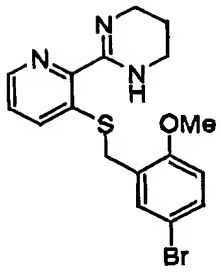
Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-21 and 26-34 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 1, 2, and 34 have been amended to comply with the Examiner's suggestions. Withdrawal of the rejection is requested.

Rejections under 35 U.S.C. § 102(b)

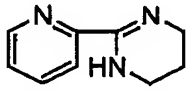
Claims 1, 3-9 and 14-18 were rejected under 35 U.S.C. § 102(a) as being anticipated by Maguire. The Examiner indicated that the claimed compounds read on compounds DF (page 108) and IE (page 121). Compound DF and compound IE have the following chemical structures.

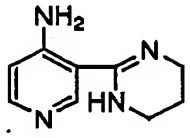




However, these compounds are clearly different from the claimed invention.

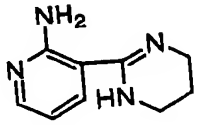
Claims 1, 3-9 and 14-18 were rejected under 35 U.S.C. § 102(b) as being anticipated by Kolaczkowska and Frei. Kolaczkowska and Frei disclose the following compounds.





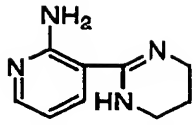
These compounds are clearly different from the claimed invention.

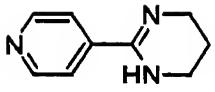
Claim 1 was rejected under 35 U.S.C. § 102(b) as being anticipated by Kwok. Kwok discloses the following compound.



This compound is clearly different from the claimed invention.

Claims 1, 3-21, and 26-34 were rejected under 35 U.S.C. § 102(b) as being anticipated by Walker and Upshall. Walker and Upshall disclose the following compounds.





However, these compounds are clearly different from the claimed invention.

Accordingly, withdrawal of the rejection of claims 1, 3-21, and 26-34 is respectfully requested.

In view of the foregoing, the application is respectfully submitted to be in condition for allowance, and prompt favorable action thereon is earnestly solicited.

If there are any questions regarding this response or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response; please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #1830/50521).

Respectfully submitted,

February 11, 2003

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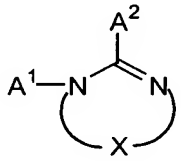
MARKED-UP VERSION TO SHOW CHANGES

IN THE CLAIMS

1. (Amended twice) A compound ~~Cyclic amidine compounds~~ represented by the formula (I):



(I)

wherein:

A^1 and A^2 are each a hydrogen atom, optionally substituted alkyl group; optionally substituted aryl group; or optionally substituted heterocyclic group; and

X is $-C(R^1,R^2)-C(R^3,R^4)-$, $-C(R^5)=C(R^6)-$, $-C(R^7,R^8)-C(R^9,R^{10})-C(R^{11},R^{12})-$, or $-C(R^{13},R^{14})-C(R^{15},R^{16})-NH-$, wherein, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each a hydrogen atom; halogen atom; optionally substituted alkyl group; optionally substituted aryl group; or optionally substituted heterocyclic group;

or pharmaceutically acceptable salt ~~salts~~ thereof.

2. (Amended) The following compounds represented by the formula (I) of claim 1;

2-(6-chloro-3-pyridyl)-2-imidazoline;

2-(6-chloro-3-pyridyl)-1,4,5,6-tetrahydropyrimidine;

2-(6-chloro-3-pyridyl)-1-methyl-2-imidazoline;

2-(6-chloro-3-pyridyl)-1-methyl-1,4,5,6-tetrahydropyrimidine;

1-(6-chloro-3-pyridyl)methylimidazole;

2-(6-chloro-3-pyridyl)imidazole;

2-(6-chloro-3-pyridyl)methyl-2-imidazoline;

2-(6-chloro-3-pyridyl)methyl-1,4,5,6-tetrahydropyrimidine;

2-(6-chloro-3-pyridyl)methyl-1-methyl-2-imidazoline;

2-(6-chloro-3-pyridyl)methyl-1-methyl-1,4,5,6-tetrahydropyrimidine;

1-(6-chloro-3-pyridyl)methyl-2-methyl-2-imidazoline;

1-(6-chloro-3-pyridyl)methyl-4,4-dimethyl-2-imidazoline;

2-(tetrahydrofuran-3-yl)-1,4,5,6-tetrahydropyrimidine;

2-(tetrahydrofuran-3-yl)-2-imidazoline;

2-(tetrahydrofuran-3-yl)methyl-1,4,5,6-tetrahydropyrimidine;

2-(5-bromo-3-pyridyl)methyl-1,4,5,6-tetrahydropyrimidine;

2-(5-bromo-3-pyridyl)methyl-2-imidazoline;

2-(3-pyridyl)methyl-1,4,5,6-tetrahydropyrimidine;

2-(3-pyridyl)methyl-2-imidazoline;

2-(3-aminophenyl)-1,4,5,6-tetrahydropyrimidine;

2-(3-quinolyl)methyl-1,4,5,6-tetrahydropyrimidine;

2-(2-chloro-5-thiazolyl)-1,4,5,6-tetrahydropyrimidine;

2-(3-quinolyl)methyl-2-imidazoline;

2-(2-chloro-5-thiazolyl)-2-imidazoline;

2-(3-quinolyl)-1,4,5,6-tetrahydropyrimidine;

2-(3-furanyl)methyl-2-imidazoline;

1-(6-chloro-3-pyridyl)methyl-1,4,5,6-tetrahydropyrimidine;

2-(3,5-dimethyl-4-isoxazolyl)methyl-1,4,5,6-tetrahydro-pyrimidine;

2-(3,5-dimethyl-4-isoxazolyl)methyl-2-imidazoline;

2-(3-thienyl)methyl-1,4,5,6-tetrahydropyrimidine;

2-(3-thienyl)methyl-2-imidazoline;

2-methyl-5-(3-pyridyl)-2-imidazoline;

5-(3-pyridyl)-2-imidazoline;

1,2-bis[(6-chloro-3-pyridyl)methyl]-1,4,5,6-tetrahydro-pyrimidine;

1-(6-chloro-3-pyridyl)methyl-2-(3-pyridyl)-2-imidazoline;

2-(5,6-dichloro-3-pyridyl)methyl-1,4,5,6-tetrahydropyrimidine;

2-(6-chloro-3-pyridyl)methyl-5-phenyl-1,4,5,6-tetrahydro-prymidine;

2-(4-pyridyl)methyl-1,4,5,6-tetrahydropyrimidine;

2-(2-chloro-3-pyridyl)methyl-1,4,5,6-tetrahydropyrimidine;

2-(2,6-dichloro-3-pyridyl)methyl-1,4,5,6-tetrahydropyrimidine;

2-[2-(6-chloro-3-pyridyl)ethyl]-1,4,5,6-tetrahydropyrimidine;

2-[2-(6-chloro-3-pyridyl)ethyl]-2-imidazoline;

2-(6-methyl-3-pyridyl)methyl-1,4,5,6-tetrahydropyrimidine;

1,2-bis[(6-chloro-3-pyridyl)methyl]-2-imidazoline;

2-(6-methyl-3-pyridyl)methyl-2-imidazoline;

2-(6-ethoxy-3-pyridyl)methyl-1,4,5,6-tetrahydropyrimidine;

2-(6-ethoxy-3-pyridyl)methyl-2-imidazoline;

2-(6-fluoro-3-pyridyl)methyl-1,4,5,6-tetrahydropyrimidine;

2-(5,6-dichloro-3-pyridyl)methyl-2-imidazoline;

2-(6-chloro-3-pyridyl)methyl-5,5-dimethyl-1,4,5,6-tetrahydro-pyrimidine;

2-(2-pyridyl)methyl-1,4,5,6-tetrahydropyrimidine;

1-(5,6-dichloro-3-pyridyl)methyl-1,4,5,6-tetrahydropyrimidine;

2-(5,6-dichloro-3-pyridyl)methyl-1-methyl-2-imidazoline;

2-(6-chloro-3-pyridyl)methyl-4-methyl-1,4,5,6-tetrahydro-pyrimidine;

1-[2-(6-chloro-3-pyridyl)ethyl]-1,4,5,6-tetrahydropyrimidine;

1-(3-pyridazinyl)methyl-1,4,5,6-tetrahydropyrimidine;

1-(6-methyl-3-pyridyl)methyl-1,4,5,6-tetrahydropyrimidine;

1-(3-pyridyl)methyl-1,4,5,6-tetrahydropyrimidine;

3-(6-chloro-3-pyridyl)methyl-1,4,5,6-tetrahydro-1,2,4-triazine;

2-[1-(6-chloro-3-pyridyl)ethyl]-1,4,5,6-tetrahydropyrimidine;

1-(2-chloro-5-thiazolyl)methyl-1,4,5,6-tetrahydropyrimidine;

1-[2-(6-chloro-3-pyridyl)ethyl]-2-methyl-2-imidazoline;

1-[2-(6-chloro-3-pyridyl)ethyl]-4,4-dimethyl-2-imidazoline;

2-(2-chloro-5-thiazolyl)methyl-1,4,5,6-tetrahydropyrimidine;

2-(2-chloro-5-thiazolyl)methyl-2-imidazoline;

2-(5-pyrimidyl)methyl-1,4,5,6-tetrahydropyrimidine;

2-(5-pyrimidyl)methyl-2-imidazoline; and

2-(5-methyl-3-pyridyl)methyl-1,4,5,6-tetrahydropyrimidine.

and pharmaceutically acceptable salt thereof.

22. (Amended) A composition according to claim 3 ~~or 4~~, further comprising a pharmaceutically acceptable carrier or excipient for oral or parenteral administration.

34. (Amended) The compound ~~Compounds~~ according to claim 1, wherein the pharmaceutically acceptable salt is a salt of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, fumaric acid, maleic acid, oxalic acid, citric acid, tartaric acid, malic acid, lactic acid, succinic acid, benzoic acid, methanesulfonic acid, and p-toluenesulfonic acid.